Menopausal Estrogen Use and Risk of Breast Cancer

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To assess the relationship of menopausal estrogens to breast cancer risk, the authors conducted a
case-control study among 881 cases and 863 controls identified through the Breast Cancer Detection
Demonstration Project (BCDDP). Use of estrogens was associated with a relative risk (RR) of 1.24
(95% C.I. 1.0–1.5), with higher risks observed among users of high-dose preparations. Hormone
effects predominated among women who received them following bilateral oophorectomy
(RR = 1.54), obliterating the protective effect normally associated with the operation. In this group,
risk increased with years of estrogen use, reaching risks of 2–3 for users of ten or more years.
High risks were also observed among oophorectomized women who used hormones in the presence of
other risk factors, including nulliparity, family history of breast cancer, and benign breast disease.
These results suggest a possible, although complex, relationship between estrogen use and risk of breast
cancer.

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REPORTS LINKING MENOPAUSAL ESTROGENS to endometrial cancer[2,11,20] have raised concern that these hormones may predispose women to breast cancer, particularly since endogenous estrogens appear to be involved in the origin of both cancers.[7,14] Cohort studies[5,10,13,22,23] and case-control studies[6,19,24] have generally shown no relationship between estrogen use and risk of breast cancer. In most investigations, however, there were limitations in the amount of exposure data, in the observation times since first exposure (latency), and in the analytic methods used. Two recent studies have demonstrated excess risks of breast cancer associated with menopausal estrogen use. Hoover *et al.*[12] in a retrospective cohort study observed that the relative risks increased with follow-up duration, progressing to 2.0 after 15 years. A case-control study by Ross and others[18] also revealed an elevated risk, primarily among women whose normal ovarian function was supplemented with large cumulative estrogen dosages. To assess further the relationship of estrogen use to risk of breast cancer, we conducted a case-control study among participants in a nationwide breast cancer screening program.

Methods

The study population was selected from a multicenter screening program, the Breast Cancer Detection Demonstration Project (BCDDP). This program recruited approximately 280,000 asymptomatic women aged 35–74 years from 29 centers across the U. S. for annual screening over a five-year period by physical examination, mammography, and thermography.

We identified women in whom breast cancer was detected between July 1973 and May 1977 from 28 of the centers. These women were individually matched with other screening subjects for whom biopsy was not recommended. The matching factors were center, race (white, black, Oriental, and other), age (within same five year group), time of entry to the screening program (within same six month period), and duration of participation in the screening program.

These women were interviewed in their homes by uniformly trained nurses. Completed interviews were obtained from 1552 cases (86% of identified subjects) and 1375 controls (74%). Women interviewed were found to be similar to those not interviewed in a number of characteristics obtained for each screening

TABLE 1. Breast Cancer Cases and Controls by Type of Menopause

	Cases (n = 881)		Controls (n = 863)	
	N	%	N	%
Natural menopause	505	57.3	481	55.7
Surgical menopause	376	42.7	382	44.3
Ovaries intact	156	17.7	133	15.4
One ovary removed	47	5.3	58	6.7
Both ovaries removed	158	17.9	177	20.5
Unknown status	15	1.7	14	1.6

subject at time of entry to the Project; these variables included age, race, family income, and history of breast surgery. The majority (74%) of the women with breast cancer were interviewed within three years after time of diagnosis. In the analyses, exposures of cases were considered only to the time of diagnosis, and exposures of controls to the time of diagnosis of the matched case.

The present analysis is confined to white women (91% of the women interviewed) who reported having undergone menopause either naturally or surgically at least one year before the date of diagnosis (equivalent date for controls). The type of menopause was defined by the event that caused the cessation of menstruation, regardless of subsequent events. The menopausal women consisted of 881 cases and 863 controls.

The relative risk (RR) associated with various factors was estimated by the odds ratio. Effects of confound-

TABLE 2. Hormone-Associated Breast Cancer Relative Risks among Menopausal Women according to Ovarian Status

	Ovarian status		
	Ovaries retained	Ovaries removed	Total
Hormone use			
Never used	1.00 (330, 336)	1.00 (32, 48)	1.00 (362, 384)
Ever used	1.20 (323, 375)	1.54 (125, 126)	1.24 (448, 401)
95% CI	(0.9–1.5)	(0.9–2.8)	(1.0–1.5)
Years used			
<5	1.16 (156, 142)	1.38 (46, 46)	1.19 (202, 188)
5–9	1.24 (88, 72)	1.55 (39, 40)	1.29 (127, 112)
10+	1.08 (73, 58)	1.70 (38, 39)	1.21 (111, 97)
χ_1 for linear trend	1.44 (P = 0.08)	1.39 (P = 0.08)	1.93 (P = 0.03)
Years since initially used			
<10	1.33 (179, 146)	1.60 (68, 60)	1.37 (247, 206)
10+	1.09 (134, 114)	1.37 (56, 63)	1.15 (190, 177)
χ_1 for linear trend	1.25 (P = 0.11)	1.16 (P = 0.12)	1.64 (P = 0.05)

Numbers in parentheses represent number of cases, number of controls.
Relative risks adjusted for age, age at menopause, and additionally for type of menopause in total group.
Unknowns excluded from analysis.

ing variables were taken into account by means of stratification. For dichotomous exposures, maximum likelihood estimates of combined relative risks and 95% asymptotic confidence limits around these estimates were derived.[9] When multiple levels of exposure were involved, one-tailed significance tests of linear trends in risk were calculated using the Mantel extension of the Mantel-Haenszel procedure.[15]

Since matching was employed in the study design, analyses were also conducted by using a matched approach.[8,16] The results were similar to those provided by the unmatched approach. However, cases were not matched to controls on menopause status, a variable used to define the current study population. In addition, the analyses of estrogen use involved control for a variety of other variables not included in the matching design. For this reason, analyses disregarding the individual matching were chosen for the majority of analyses and for presentation.

Results

A preliminary evaluation of reported menopausal hormone use among these women revealed no association with risk of breast cancer. Fifty-four percent of the cases and 52% of the controls reported ever use, resulting in a nonsignificant age-adjusted risk estimate of 1.10. In addition, no distinctive trends were seen either according to years of use or years since initial use. Risks were similar for users of less than five years time (RR = 1.07) and users of ten or more years (RR = 1.04), and no increase in risk was observed among women whose use of estrogens began ten or more years before diagnosis (RR = 1.01).

Since ovarian status is known to influence both the risk of breast cancer[21] as well as rates of exposure to menopausal estrogens,[17] we decided to pursue analyses further by examining hormone use in relation to the type of menopause experienced. Table 1 shows the distribution of cases and controls by type of menopause. Slightly more than half of the subjects reported having undergone a natural menopause (505 patients and 481 controls). A total of 376 patients and 382 controls reported having had a surgical menopause. A bilateral oophorectomy was reported by approximately 20% of the menopausal women, while a hysterectomy alone was reported by about 15%. A small number of women (47 patients and 58 controls) indicated having had a surgical menopause involving a unilateral oophorectomy. Since these women were found to differ from the other menopausal women on a variety of factors, including hormone use, we decided to exclude them from analysis until accumulation of additional numbers. The 15 patients and 14 controls whose ovarian status

was unknown were also removed from the present analysis.

In addition to considering ovarian status in relation to hormone use, it was necessary to evaluate the influence of potential confounding variables. We found increased risks of breast cancer associated with the reporting of a family history of breast cancer, late age at first childbirth, early age at menarche, late menopause, and history of previous breast biopsy. All of these characteristics were associated to some extent with rates of hormone exposure, but only age at menopause exerted any confounding influence. This was found to be a negative confounder to hormone associations, particularly quantitative measures of hormone use: that is, younger ages at menopause were associated with lower risks of breast cancer but higher rates of hormone use, especially extended durations of use. Thus, it was important to account for the influence of age at menopause in subsequent analyses.

Table 2 presents risk estimates for hormone use after adjustment for age at diagnosis, age at menopause, and type of menopause (natural, hysterectomy alone, and hysterectomy with bilateral oophorectomy). The relative risk associated with ever use of menopausal hormones was 1.24 (95% CI 1.0–1.5). The excess risk associated with use of estrogens was highest among those women who received them following a bilateral oophorectomy. Use of hormones among these women was associated with a relative risk of 1.54 (0.9–2.8), while in women whose menopause did not involve removal of ovaries (natural menopause or hysterectomy alone) the risk was 1.20 (0.9–1.5). While there was a statistically significant increasing linear trend in the relative risk with years of hormone use in the total group, this derived primarily from the difference between users and nonusers, as there was no apparent trend in risk by years of use among the users. However, among those women having undergone a bilateral oophorectomy, there was evidence of an increase in relative risk with increasing years of use, rising to 1.70 for those who used estrogens for ten or more years.

Further analyses evaluated the relationship of medication dose and regimen to risk of breast cancer (Table 3). To assess the effects of dose, we examined different dosages of Premarin®, a conjugated estrogen. This was the most commonly reported medication (accounting for 74% of reported estrogen use). Since the four different dosages of Premarin are marketed as distinct colors, we felt that the study subjects should have been able to provide reasonably accurate information about dosages received. This

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® Conjugated estrogen tablets, U.S.P., Ayerst, New York, NY.

TABLE 3. Breast Cancer Relative Risks by Dose and Regimen of Estrogen Use

	Ovarian status		
	Ovaries retained	Ovaries removed	Total
Dose of Premarin used most recently			
Premarin 0.3 mg	0.64 (18, 28)	0.57 (3, 7)	0.63 (21, 35)
Premarin 0.6 mg	1.14 (73, 63)	1.30 (20, 24)	1.17 (93, 87)
Premarin 1.25 mg	1.19 (114, 96)	1.64 (60, 50)	1.27 (174, 146)
Premarin 2.5 mg	2.89 (5, 2)	1.74 (4, 4)	2.21 (9, 6)
Premarin—unknown dose	1.78 (16, 9)	3.04 (4, 2)	1.97 (20, 11)
Dose of Premarin used longest			
Premarin 0.3 mg	0.77 (13, 17)	0.91 (2, 3)	0.79 (15, 20)
Premarin 0.6 mg	1.22 (69, 56)	2.12 (19, 13)	1.34 (88, 69)
Premarin 1.25 mg	1.10 (129, 116)	1.51 (67, 66)	1.18 (196, 182)
Premarin 2.5 mg	2.45 (6, 3)	1.23 (5, 6)	1.70 (11, 9)
Premarin—unknown dose	1.29 (13, 10)	3.04 (4, 2)	1.53 (17, 12)
Regimen of hormone used longest			
Every day	1.21 (95, 78)	1.77 (56, 43)	1.32 (151, 121)
Every other day	0.97 (10, 10)	2.06 (4, 3)	1.17 (14, 13)
Cyclically	1.31 (148, 115)	1.04 (35, 47)	1.26 (183, 162)
Other regimen	0.86 (52, 58)	1.40 (24, 26)	0.97 (76, 84)
Unknown regimen	1.30 (18, 14)	1.37 (6, 7)	1.32 (24, 21)

Numbers in parentheses represent number of cases, numbers of controls.
All risks relative to nonusers.
Relative risks adjusted for age, and additionally for type of menopause in total group.

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analysis demonstrated an increasing trend in risk with increasing medication dosage. When the most recently used medication was considered, risk was found to be lowest (0.63) for users of pills containing 0.3 mg of estrogen, and highest (2.21) for users of the highest dosage, 2.5 mg. A similar trend in risk was observed for the hormone reportedly used for the longest period of time, with risks varying from 0.79 for the lowest dose medication to 1.70 for the highest dose. The same relationships appeared to prevail for the most part within the separate menopause groups.

In contrast to the relationships with estrogen dose, no clear associations were observed overall by the regimen of medication used for the longest period of time. The majority of women reported using these medications either every day or cyclically (three weeks on, one week off). Risks were similar for these two regimens—1.32 and 1.26, respectively. Among the bilaterally oophorectomized women, there was some indication that use every day conferred a higher risk (1.77) than did use on a cyclical basis (1.04). However, these two estimates were not significantly different from each other.

When the effects of estrogen use were considered in relation to other risk factors, several interactions were suggested in women with a bilateral oophorectomy (Table 4). In nulliparous women, the risk associated with hormone use was 5.54 (1.3–24.6), an estimate considerably higher than that observed among parous

TABLE 4. Hormone-Associated Breast Cancer Relative Risks by Selected Breast Cancer Risk Factors among Women with Bilateral Oophorectomy

	Cases (n = 158)	Controls (n = 177)	Relative risk (95% C.I.)
Parity			
0	26 (92)	38 (68)	5.54 (1.3–24.6)
1–2	81 (77)	85 (72)	1.28 (0.6–2.6)
3+	48 (77)	51 (76)	1.03 (0.4–2.7)
Family history of breast cancer in mother			
No	133 (77)	164 (72)	1.28 (0.8–2.2)
Yes	21 (95)	8 (75)	6.67 (0.6–71.0)
Breast biopsy			
No	124 (77)	136 (71)	1.38 (0.8–2.4)
Yes	33 (88)	38 (76)	2.25 (0.6–8.0)
1	23 (83)	28 (79)	1.30 (0.3–5.3)
2+	10 (100)	10 (70)	∞ (1.1–∞)

Numbers in parentheses represent percent of patients or controls in each risk factor category who reported usage of hormones.

Relative risks represent risk of ever use of menopausal hormones vs. no use within each risk category. Risks presented are unadjusted; age adjusted risks virtually identical.

Unknowns excluded from analysis.

women. Women who reported having a history of breast cancer in their mothers also reported higher hormone-associated risks (6.67) than those without such a history (1.28). In addition, history of a previous breast biopsy seemed to enhance the effects of hormone use, particularly when multiple breast biopsies were reported. No consistent interactions were seen with age at first livebirth, age at menopause, and age at first use of hormones. Interactions between hormone use and breast cancer risk factors were not observed among the women without a bilateral oophorectomy.

A final analysis focused on hormone use among breast cancer cases detected on the second or later screening examinations (Table 5). Overall, the relative risk associated with ever use of estrogens was similar (1.22) to that seen for the total case series. However, among the bilaterally oophorectomized women, the risk was 3.14, an estimate considerably higher than that observed previously. In addition, risk increased significantly with years of hormone use, reaching 3.42 ($P < 0.05$) for users of ten or more years. In addition, among the bilaterally oophorectomized women, there was some indication of an increasing trend in risk with time since initial use.

Risks associated with hormone use according to different menopause categories were also derived by means of matched[3] and unmatched[1] multivariate analyses. These took into account the simultaneous influence of several potentially confounding variables.

Risk estimates were similar to those of the stratified analyses.

Discussion

This case-control study revealed the complexities of evaluating the relationship between menopausal hormone use and risk of breast cancer. Associations between estrogen use and breast cancer risk were found to be dependent on evaluations of interactive and confounding factors. In particular, it was important to consider the confounding effects of age at menopause on quantitative measures of use and to distinguish effects of hormone use by ovarian status.

After adjustment for these factors, hormone use was found to be associated with a statistically significant relative risk of 1.24. The excess risk seemed to derive predominantly from high risks among women who received estrogens following bilateral oophorectomy. In the total case series of bilaterally oophorectomized women, the risk of breast cancer following use of menopausal hormones was elevated approximately 50%. An increased trend in risk was observed with years of estrogen use, with users of ten or more years demonstrating nearly a twofold excess risk. In addition, among the bilaterally oophorectomized women, the highest risks were observed when hormones were used in the presence of known risk factors, including nulliparity, maternal history of breast cancer, and history of a previous breast biopsy. The elevated risk among women with a previous breast biopsy is consistent with previous observations regarding estrogen use,[12,18] while the potentiation of hormone effects among women with a family history of breast cancer is consistent with an interaction observed for oral contraceptive use.[4] These hormone interactions may reflect the capacity of estrogens to act as cocarcinogens or promoters.

The findings of the highest risks of hormone use among women having undergone a bilateral oophorectomy directly contradicts the findings of Ross et al.[18] who observed excess risks confined to women with intact ovaries. While our results are not readily reconciliable with theirs, we think the strongest effects of estrogen use among the bilaterally oophorectomized women in our study may be due to hormone effects being able to be more clearly exerted in those with a lower risk for the disease. In support of this was the finding that hormone use obliterated the protective effect normally associated with a bilateral oophorectomy. Those women who did not receive hormones in conjunction with a bilateral oophorectomy

were at a significantly lower risk (0.57) than similarly aged women who underwent a natural menopause unassisted by hormones. In contrast, those women with a bilateral oophorectomy who received estrogens experienced no reduction in risk (1.05).

The highest risks associated with hormone use among the bilaterally oophorectomized women were seen when analysis considered only those breast cancer cases detected after the initial screening examination. A three-fold elevation of risk was associated with ever use of hormones, increasing to nearly four-fold among long-term users. Since cases detected on a second or later screening examination are more likely to represent a true incident case series, they may offer an improvement over the total series for evaluating etiologic factors. Alternatively, there may be differences in the type of disease detected on an initial screening exam compared with later exams (*e.g.*, stage, size, histology). The significance of this finding is being pursued in our continuing study of BCDDP data.

Since excess risks seemed to predominate in the subgroup of women who had undergone a bilateral oophorectomy, we felt it necessary to consider whether our findings might be due to various forms of bias. A major concern was that findings depended on classifications of ovarian status and hormone use based on patient interviews. For a sample of patients, we checked information on ovarian status against hospital discharge summaries, operative reports, and pathology reports. The rates of agreement between cases and controls were similar but varied according to the number of ovaries reported by the patient to have been removed (95% agreement rate for those reporting only a hysterectomy, 83% for those reporting a bilateral oophorectomy, and 77% for those reporting a hysterectomy with unilateral oophorectomy). In addition, validation of the histories of recent hormone use against physician records showed identical rates of agreement for cases and controls (94% each) and no evidence of the cases reporting biased medication dosages. Since misclassification of ovarian status and estrogen use appeared to be similar for cases and controls, we were assured that our findings did not result from biased reporting. In fact, any effect of the misreporting would have been in the direction of obscuring real associations regarding hormone use.

Consideration was also given to the source of the study population, since participants in the screening program were not a random sample of the population, but rather a self-selected group. Previous investigation of this issue has demonstrated that these women appear to be an appropriate resource for evaluating

TABLE 5. Hormone-Associated Breast Cancer Relative Risks by Ovarian Status among Cases Detected after the Initial Screening Examination

	Ovarian status		
	Ovaries retained	Ovaries removed	Total
Hormone use			
Never used	1.00 (114, 114)	1.00 (7, 17)	1.00 (121, 131)
Ever used	1.08 (122, 118)	3.14 (45, 48)	1.22 (167, 166)
95% C.I.	(0.7–1.6)	(0.9–11.2)	(1.0–1.5)
Years used			
<5	1.00 (63, 66)	1.77 (18, 19)	1.08 (81, 85)
5–9	1.31 (37, 28)	3.21 (12, 12)	1.50 (49, 50)
10+	0.84 (20, 22)	3.42 (15, 17)	1.17 (35, 39)
χ_l for linear trend	0.15 (P = 0.44)	1.70 (P = 0.04)	0.91 (P = 0.18)
Years since initially used			
<10	1.29 (80, 66)	2.32 (24, 22)	1.35 (104, 88)
10+	0.79 (38, 45)	2.88 (21, 25)	1.00 (59, 70)
χ_l for linear trend	−0.33 (P = 0.37)	1.64 (P = 0.05)	0.35 (P = 0.36)

Analysis includes cancer patients detected after the initial screening examination and control subjects originally matched to such cancer patients.

Numbers in parentheses represent number of cases, number of controls.

Relative risks adjusted for age, age at menopause, and additionally for type of menopause in total group.

Unknowns excluded from analysis.

etiologic relationships.[4] In the present study, there is no reason to suspect that selection biases would have created systematic differences between the cases' and controls' use of hormones. It is also unlikely that selection factors could have accounted for our observations of highest risk among those at a low risk of disease, *i.e.*, the bilaterally oophorectomized women. It remains to be seen whether our results can be generalized to other populations of women. Although the findings confirm recent reports that estrogen use may increase the risk of breast cancer, the relationships are complex and need further evaluation.

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